CCCXVIII.—*Researches in the Menthone Series. Part VII. The Condensation of Menthylamines with* d- *and* l-*Oxymethylenecamphor.*

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THE only complete optical resolutions of externally compensated menthylamines which have yet been recorded are those of *dl*-menthylamine and *dl-neo*menthylamine by means of the hydrogen *d*-tartrates (J., 1929, 23). The unusual difficulties which we experienced in attempting the resolution of menthylamines with optically active acids (*loc. cit.*) led us to study the possibility of utilising optically active oxymethylenecamphor as a resolving agent in this field. This reagent reacts readily with the bases, and from *dl-neo*menthylamine we found it possible to prepare optically pure specimens of the *d*- and *l*-base with the aid of *d*-oxymethylenecamphor only. Owing to their great solubility, the condensation products furnished by *dl-iso*menthylamine and *dl*-menthylamine could not be submitted to fractional crystallisation, so that no resolution could be effected in these instances.

The further possibility was envisaged that the *d*- and *l*-forms of a particular menthylamine might display different velocities of reaction with *d*-oxymethylenecamphor. In such an event, the residual base from an interaction between a *dl*-base and this reagent should be optically active, as in the case of *dl-ac*-tetrahydroquinaldine (Pope and Read, J., 1913, **103**, 1528). In none of the three reactions examined, however, was any measurable optical activity displayed by the unchanged base. Thus, the optical resolution of *dl-iso*menthylamine still remains an unsolved problem.

The preparation and characterisation of stereochemically homogeneous substances of the types *d*-*D* and *d*-*L* was rendered possible by condensing an optically pure *d*- or *l*-menthylamine (indicated by *d*- or *l*- in the abbreviated representation) with an optically pure *d*- or *l*-oxymethylenecamphor (indicated by *D* or *L*). The optical resolution of *dl-neo*menthylamine is possible because a mixture of the diastereoisomeric derivatives *d*-*D* and *l*-*D* may be separated by fractional crystallisation. Pope and Read (*loc. cit.*, p. 1516) showed that in certain instances pairs of substances related in this way were capable of forming partial racemates, and that in solution these partial racemates exhibited rotatory powers which were the mean of those of their components. The conclusion was therefore drawn that no " combination exists in the solution between the two components of the partially racemic substance which exists in the crystalline condition as a definite compound " (p. 1522).

With *dl*-menthylamine, there is no evidence regarding the practicability or otherwise of separating the substances *d*-*D* and *l*-*D*, owing to the great solubility of the material; but the observed rotatory power of the mixture, $[\alpha]_D$ + 140·2°, approximates so closely to the calculated value, $[\alpha]_D$ + 133·5°, as to render unlikely the existence of a combination between its constituents in solution. *dl-iso*Menthylamine, however, appears to present a new kind of behaviour; for here the observed values of $[\alpha]_D$ for the equimolecular mixture of *d*-*D* and *l*-*D* is + 162·2°, whereas the mean of the values for the individual components is (+ 212·9° + 281·3°)/2 = + 247·1°. The marked discrepancy between the observed and the calculated rotatory powers points to the conclusion that the diastereoisomerides *d*-*D* and *l*-*D* in this case form a partially racemic combination, the stability of which persists even in an alcoholic solution.

The interesting observation that mutarotation was displayed by some, but not all, of these stereoisomeric condensation products adds to the difficulty of advancing a satisfactory explanation of this striking property of so many methylenecamphor derivatives (compare J., 1909, **95**, 179).

EXPERIMENTAL.

1. neo*Menthylamines*. — *d-neo*Menthylamine hydrochloride (J., 1926, 2219), having $[\alpha]_D$ + 21·5° in water, was treated with sodium hydroxide in aqueous solution; the liberated base was then extracted with ether and dissolved in an excess of 50% acetic acid. When this solution was mixed on the water-bath with a warm alcoholic solution of *d*-oxymethylenecamphor (1 mol.; *Annalen*, 1894, **281**, 331), an oily separation of the condensation product

occurred almost at once. After about 10 minutes the derivative was isolated in ether and washed free from unchanged materials in the usual way (J., 1913, **103**, 1516). A crystalline mass was obtained when the solvent was removed in a vacuum and the residue kept in a desiccator for several days. The product dissolved readily in all the usual organic solvents except light petroleum; since crystallisation could not be effected from solutions in warm light petroleum, the substance was purified by washing it with the cold solvent until a constant specific rotatory power was attained. d-neo*Menthylamino*-d-*methylenecamphor* forms small colourless crystals, m. p. 105°, $[\alpha]_D$ + 317·8° in absolute alcohol (*c* 0·6 g. in 100 c.c.; $l = 2$; $t = 16°$); no mutarotation was observed after 48 hours (Found: C, 79·4; H, 10·9. $C_{21}H_{35}ON$ requires C, 79·5; H, 11·0%).

d-neo*Menthylamino*-l-*methylenecamphor*, prepared similarly from the same base and *l*-oxymethylenecamphor (J., 1913, **103**, 445), crystallised from light petroleum in colourless translucent prisms, m. p. 94°, $[\alpha]_D$ − 129·8° in absolute alcohol (*c* 0·6); no mutarotation was observed after 48 hours (Found: C, 79·6; H, 10·8%)

When equimolecular quantities of *dl-neo*menthylamine and *d*-oxymethylenecamphor were condensed in the same way, the crude product was obtained in transparent prisms (m. p. 92°) embedded in a viscid syrup. The mixture was stirred and kept for several days in a desiccator in the ice-chest; the whole mass then became crystalline, but it could not be recrystallised from a solvent. Accordingly, it was well washed with cold light petroleum. The undissolved portion consisted of pure *d-neo*menthylamino-*d*-methylenecamphor, m. p. 105°, $[\alpha]_D$ + 317·4° in absolute alcohol (*c* 0·6). The petroleum washings deposited crystals which after recrystallisation from the same solvent yielded pure l-neo*menthylamino*-d-*methylenecamphor*, m. p. 92°, $[\alpha]_D$ + 130·0° in absolute alcohol (*c* 0·6); this substance showed no mutarotation (Found: C, 79·4; H, 11·1%).

When dissolved in rectified spirit and titrated with bromine (1 mol.), *d-neo*menthylamino-*d*-methylenecamphor underwent the usual reaction (J., 1913, **103**, 448). After evaporation to small bulk on the water-bath, the product was shaken with water and benzene; the aqueous layer deposited d-neo*menthylamine hydrobromide* upon evaporation to dryness (Found: Br, 33·7. $C_{10}H_{21}N,HBr$ requires Br, 33·9%). This salt crystallised from ethyl acetate in long lustrous prisms which did not melt below 220°; $[\alpha]_D$ + 18·6°, $[M]_D$ + 44° in aqueous solution (*c* 0·6). *l-neo*Menthylamino-*d*-methylenecamphor similarly yielded *l-neo*menthylamine hydrobromide, $[\alpha]_D$ − 18·5°, $[M]_D$ − 44° in water. *dl-neo*Menthylamine

hydrobromide (J., 1926, 2229) is considerably less soluble than its optically active components.

As only about 76% of the *dl-neo*menthylamine and *d*-oxymethylenecamphor condensed in the above reaction, the unchanged base was recovered from the acid washings in the form of hydrochloride: 1·1960 g., made up to 20 c.c. with water, gave no appreciable deviation in a 2-dcm. tube when examined in sodium light.

2. iso*Menthylamines*.—When prepared in the usual way, d-iso*menthylamino*-d-*methylenecamphor* was obtained as a syrup which crystallised to a hard mass when kept in an evacuated desiccator in the ice-chest for several days. It could not be recrystallised from any solvent, but when washed with cold light petroleum it yielded microscopic crystals, m. p. 110°. It displayed mutarotation in absolute alcoholic solution (*c* 0·6), the original value, $[\alpha]_D$ + 281·3°, changing to + 274·9° in 15 hours, and attaining the constant value, + 257·5°, in 48 hours (Found: C, 79·3; H, 11·2%).

d-iso*Menthylamino*-l-*methylenecamphor* was also obtained as a syrup which crystallised with difficulty. After being washed with cold light petroleum, the substance melted at 99—100°; in absolute alcohol (*c* 0·6) it gave $[\alpha]_D$ — 212·9°, changing to — 179·6° in 15 hours, and attaining the constant value, — 160·8°, in 48 hours (Found: C, 79·3; H, 11·3%).

The product furnished by the condensation of *dl-iso*menthylamine (J., 1926, 2230) with *d*-oxymethylenecamphor (1 mol.) was a syrup which could not be induced to crystallise, even when seeded with crystals of each of the two derivatives just described; no separation of this material into component substances could thus be brought about. The product exhibited mutarotation in absolute alcohol (*c* 0·8), the initial value, $[\alpha]_D$ + 162·2°, changing to the constant value, + 155·2°, in 48 hours. The unchanged *iso*menthylamine recovered from the acid washings in this experiment was optically inactive: 1·0003 g. of the hydrochloride, made up to 20 c.c. with water, gave no rotation when examined in a 2-dcm. tube in sodium light.

3. *Menthylamines*. — l-*Menthylamino*-d-*methylenecamphor*, prepared as usual, was obtained as a crystalline mass after removal of the ether. This product melted indefinitely at 65—75°, and showed mutarotation in absolute alcohol (*c* 0·6), the original value, $[\alpha]_D$ + 75·3°, changing to + 82·9° in 1·5 hours and attaining the constant value, + 108·7°, in 16 hours. Recrystallisation was difficult; the small needles deposited from aqueous alcohol had m. p. 90°, $[\alpha]_D$ + 96·7°, changing to + 110·4° in 7 hours and becoming constant at + 125·0° in 16 hours (Found: C, 79·5; H, 11·1%).

l-*Menthylamino*-l-*methylenecamphor* consisted of a thick glassy

syrup, which crystallised partly in long slender needles on being kept in an evacuated desiccator in a cold place for a fortnight. It was very soluble in all organic solvents, and could not be recrystallised. In absolute alcohol (*c* 0·6) it gave the value $[\alpha]_D$ — 170·2°, which remained unaltered after 24 hours (Found: C, 79·0; H, 11·3%).

The crude product formed upon condensing equivalent weights of *dl*-menthylamine (J., 1926, 2226) and *d*-oxymethylenecamphor crystallised partly when kept in a desiccator, but it could not be fractionally crystallised. The original value of $[\alpha]_D$ in absolute alcohol (*c* 1·0) was + 140·2°; this changed to + 145·6° in 16 hours and then remained constant. The yield was 63% of the theoretical, and the hydrochloride of the unchanged base was optically inactive in aqueous solution (0·7130 g. in 20 c.c.).

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